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Evaluation the safety and efficacy of fractional CO_2 laser in the treatment of melasma

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Abstract
Background: Melasma, formerly known as chloasma, is an acquired pigmentary disorder that mostly affects the face. This disease, which is more common in females and darker skin types, is primarily caused by ultraviolet (UV) exposure and hormonal effects.
Aim of the study: The aim of this study was to evaluate the safety and outcomes of ablative fractional CO_2 lasers on melasma in patients with skin of color.
Patients and Methods: This prospective study, conducted from December 1, 2023, to May 2024 at the private clinics in Karbala City, involved 80 female patients aged 22-60 years with melasma. Participants provided written informed consent and were randomly assigned to two groups. Group A (n=40) received fractional CO_2 laser treatment (4 sessions, 3 weeks apart), while Group B (n=40) applied a topical 5% TXA cream nightly for 12 weeks. Exclusion criteria included autoimmune diseases, hepatitis, coagulopathies, thyroid disorders, recent use of certain medications, pregnancy, breastfeeding, and dissatisfaction with treatment techniques. Patients were diagnosed using standard criteria and Wood's light examination. All were advised to avoid sun exposure and use daily sunscreen. Efficacy was assessed through digital photographs, modified melasma area and severity index (mMASI) scores, patient satisfaction, side effects, and dermoscopic evaluations before and after treatment.
Results: Both groups had similar baseline characteristics, with no significant differences in age, disease duration, skin type, or clinical types of melasma. At 8 weeks, the CO_2 laser group showed a significantly greater reduction in mMASI scores compared to the TXA group (P=0.001). This trend continued at 12 and 16 weeks, indicating the superior efficacy of CO_2 laser treatment. Patient satisfaction was higher in the CO_2 laser group, with 45% reporting being very satisfied compared to 20% in the TXA group. The recurrence rate was lower in the CO_2 laser group (18%) than in the TXA group (30%). Side effects were fewer in the CO_2 laser group, with no cases of post-inflammatory hyperpigmentation, compared to 30% in the TXA group (P=0.003).
Conclusion: Fractional CO_2 laser treatment is more effective than topical TXA in reducing melasma severity, improving patient satisfaction, and preventing recurrence, with fewer side effects. Dermoscopic evaluations confirmed significant improvement in pigmentation and skin texture post-treatment in both groups.

Keywords: Melasma, chloasma, pigmentary disorder, facial pigmentation

1. Introduction
Melasma, formerly known as chloasma, is an acquired pigmentary disorder that mostly affects the face. This disease, which is more common in females and darker skin types, is primarily caused by ultraviolet (UV) exposure and hormonal effects. Melasma is a clinical diagnostic characterized by symmetric reticulated hypermelanosis in three primary face patterns: centrofacial, malar, and mandibular [1]. The centrofacial pattern, which affects the forehead, nose, and upper lip but not the philtrum, cheeks, or chin, is the most common clinical pattern in 50–80% of cases [2]. The malar pattern is limited to the malar cheeks of the face, whereas mandibular melasma appears on the jawline and chin. The latter is considered to occur in elderly persons and may be more associated with severe photodamage [3]. New data suggests that vascular growth factor (VEFG), solar elastosis, an increase in mast cells, and disruption of the basement membrane are all variables on the skin that may contribute to

the development of melasma. Further, the histological results reveal a rise in both the amount of melanin deposition and the number of melanocytes [1, 4].

A novel pattern known as extra-facial melasma can appear on non-facial body areas such as the neck, sternum, forearms, and upper extremities [4]. Despite its prevalence, managing this condition remains difficult because to a lack of understanding of the pathophysiology, chronicity, and recurrence rates. In addition to classic melasma treatments, there are intriguing novel options, such as topical, oral, and procedural therapy. Melasma can appear anywhere on the face and can take many different forms, ranging from superficial to deep lesions or a combination of the two. There are several laser treatments available for each kind, but the standard therapy that is universally beneficial has not yet been identified [5, 6].

Laser therapy uses light energy emitted by a laser medium. The CO_2 laser emits light energy at 10,600 nm to the fluid in tissues. However, water can also be found in the soft tissue around the target zone. The CO_2 laser selects tissues but not pigments [7]. Vaporization and ablation can immediately eradicate both pigmented and non-pigmented skin blemishes. As a result, it is critical for physicians to treat the lesion while minimizing injury to surrounding tissue [8]. CO_2 lasers are commonly used to treat superficial skin lesions, including nevus, xanthelasma, warts, and seborrheic keratosis [9].

2. Patients and methods

This prospective study was done at the private clinics in Karbala City from the 1st of December 2023 to the end of May 2024.

2.1 Patients

A total 80 female patients with melasma signed up for the study, aged 22-60 years. Prior to participation, written informed consent was obtained from all eligible participants after explaining the purpose and procedures of the study.

Patients were randomly divided into 2 equal groups.

1. Patients of group A were treated with fractional CO_2 laser (4 sessions, 3 weeks apart). Fractional CO_2 laser sessions were on the following parameters: power 8-10 W (according to the skin type, performed using CO_2 laser [SmartXide DotR-DEKA], spacing 1000 μm (5.3% density), dwell time 400 µs, and stack 1).
2. Patients of group B were treated only by topical daily night application of 5% TXA cream for 12 weeks.

2.2 Methods

Patients were clinically diagnosed with melasma by experienced dermatologists using standard diagnostic criteria. Additionally, the examination was performed using a Wood's light to determine the type of melasma (epidermal, dermal, or mixed).

All included patients were instructed to avoid sun exposure as much as possible and to apply a proper daily sunscreen (SPF + 50) throughout the treatment period. Digital photographs were taken at base line, at the end of treatment then at follow up (after 3 months of treatment end) to assess treatment efficacy and recurrence. Scoring of melasma was done by using the modified melasma area and severity index score (mMASI). Assessment of treatment efficacy was done through physician evaluation (Specialized dermatologists were asked to calculate mMASI score before and after completion of the treatment to assess percentage of improvement. Finally the minimum rate on which the three investigators agreed was considered as the investigator' s view in the study), patient satisfaction (patients were asked at the end of treatment to rate the overall satisfaction comparing with the pretreatment condition using the following grades: very satisfied (≥ 75% improvement), satisfied (50%-74%), slightly satisfied (25%-49%), and not satisfied (0%-24%). Side effects were reported throughout the treatment period and during follow up.

2.3 Dermoscopic evaluation

Skin lesions are observed in immersion mode, and the following dermoscopic features are analyzed by well-trained dermatologists with 5 years of clinical work experience in dermatology and official training in dermoscope: epidermal background state, dark brown spots/ patches, capillary condition as well as hair follicles and sweat pore characteristics.

3. Results

3.1 General properties of melasma patients who treated with CO_2 laser topical tranexamic acid

The data presented compares two groups of melasma patients, one treated with CO_2 laser and the other with topical tranexamic acid. Both treatment groups show a similar distribution in age and disease duration with p-values of 0.67 and 0.76 respectively, indicating no significant difference between the groups. The skin type distribution shows slight variations, particularly in types II and IV, but these are not statistically significant (p=0.56). Likewise, the clinical types of melisma-mixed, vascular, and pigment - show some differences in distribution between the groups, but again, these are not statistically significant (p=0.59).

Table 1: General properties of melasma patients who treated with CO_2 laser topical tranexamic acid

Characteristic	Melasma patients				P-value
	Received CO_2 laser (n=40)		Received topical tranexamic acid (n=40)		
Age (years					
<30	10	25%	12	30%	0.67
≥30	30	75%	28	70%	
Duration of the disease					
<6 y	13	33%	11	28%	0.76
≥6 y	27	68%	29	73%	
Skin type according to Fitzpatrick					
II	7	18%	4	10%	0.56
III	13	33%	13	33%	
IV	15	38%	20	50%	
V	5	13%	3	8%	

Total	40	100%	40	100%	
Clinical type					
Mixed	13	33%	20	50%	0.59
Vascular	19	48%	17	43%	
Pigment	8	20%	3	8%	
	40	100%	40	100%	

3.2 Comparison of MASI scores over time between patients received CO_2 laser versus who received topical tranexamic acid

At the baseline (0 weeks), the mean MASI scores were similar between the two groups, with no statistically significant difference (12.28±1.78 for the CO_2 laser group and 12.37±1.76 for the tranexamic acid group, P=0.56). However, as the treatment progressed, notable differences emerged. At 4 weeks, both groups showed slight improvements, but the difference remained statistically insignificant (P=0.28). By 8 weeks, the CO_2 laser group demonstrated a significantly greater reduction in MASI scores (10.67±1.66) compared to the tranexamic acid group (11.37±1.68), with a P-value of 0.001, indicating a significant improvement with the CO_2 laser treatment. This trend continued at 12 weeks and 16 weeks, where the CO_2 laser group showed dramatic reductions in MASI scores (7.98±1.78 and 5.63±1.76, respectively) compared to the tranexamic acid group (10.11±1.56 and 9.32±1.74), both with P-values of 0.001. These results highlight the superior efficacy of CO_2 laser treatment in reducing melasma severity over time, demonstrating a more pronounced and quicker improvement in skin condition compared to topical tranexamic acid.

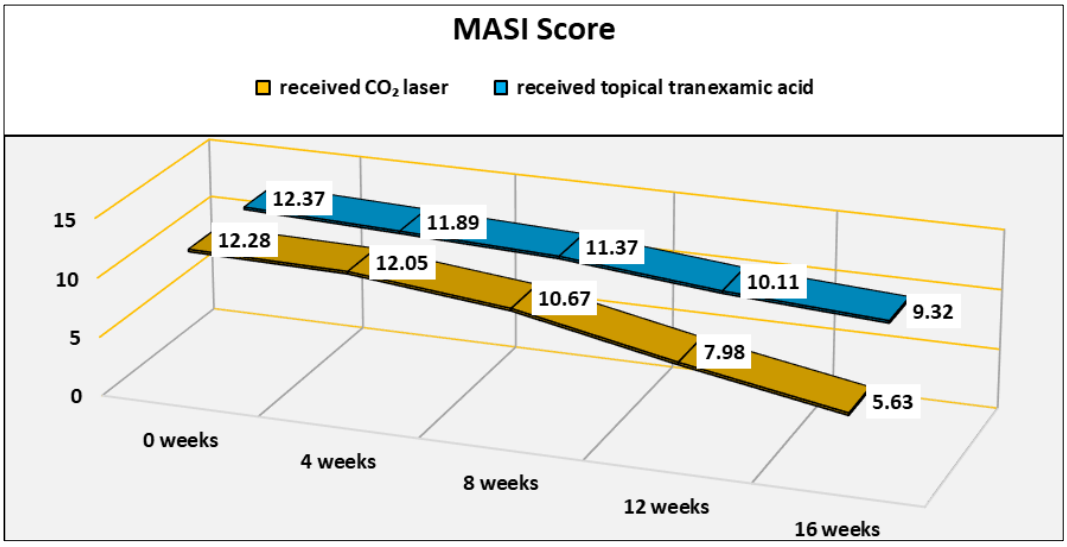


Fig 1: Comparison of MASI scores over time between patients received CO_2 laser versus who received topical tranexamic acid

Table 2: Comparison of MASI scores over time between patients received CO_2 laser versus who received topical tranexamic acid

Time of treatment	MASI Score (mean ±SD) of melasma patients		P-value
	Received CO_2 laser (n=40)	Received topical tranexamic acid (n=40)	
0 weeks	12.28±1.78	12.37 ±1.76	0.56
4 weeks	12.05±1.09	11.89±1.83	0.28
8 weeks	10.67± 1.66	11.37±1.68	0.001
12 weeks	7.98±1.78	10.11±1.56	0.001
16 weeks	5.63±1.76	9.32±1.74	0.001

3.3 Comparing patient satisfaction between melasma patients who received CO_2 laser versus topical tranexamic acid

In comparing patient satisfaction between melasma patients who received CO_2 laser treatment and those who received topical tranexamic acid, distinct differences emerge. Among the 40 patients treated with CO_2 laser, 45% (18 patients) reported being very satisfied, significantly higher compared to only 20% (8 patients) in the tranexamic acid group. This suggests a greater overall satisfaction with the CO_2 laser treatment. Conversely, the proportion of patients who were not satisfied was slightly lower in the laser group at 20% (8 patients) compared to 25% (10 patients) in the tranexamic acid group. Additionally, the percentage of patients who were satisfied (10% vs. 25%) and slightly satisfied (25% vs. 30%) were both higher in the tranexamic acid group, indicating a more moderate level of satisfaction. Overall, while the CO_2 laser treatment had a higher proportion of very satisfied patients, the tranexamic acid treatment had a higher proportion of patients in the satisfied and slightly satisfied categories. This comparison highlights that while CO_2 laser treatment may lead to higher levels of satisfaction in a subset of patients, topical tranexamic acid tends to result in more evenly distributed moderate satisfaction levels across patients.

Table 3: Comparing patient satisfaction between melasma patients who received CO_2 laser versus topical tranexamic acid

Patients satisfaction	Melasma patients			
	Received CO_2 laser (n:40)		Received topical tranexamic acid (n:40)	
	No.	%	No.	%
Not satisfied	8	20%	10	25%
Satisfied	4	10%	10	25%
Slightly satisfied	10	25%	12	30%
Very satisfied	18	45%	8	20%
Total	40	100%	40	100%

P-value: 0.047

3.4 Comparing of recurrence rates between melasma patients who received CO_2 laser versus topical tranexamic acid: The comparison of recurrence rates between melasma patients treated with CO_2 laser and those treated with topical tranexamic acid indicates a notable difference in the likelihood of recurrence. Among the 40 patients who received CO_2 laser treatment, only 18% (7 patients) experienced a recurrence of melasma, whereas a higher percentage of 30% (12 patients) was observed in the group treated with topical tranexamic acid. Conversely, 83% (33 patients) of the CO_2 laser-treated group did not experience a recurrence, compared to 70% (28 patients) in the tranexamic acid group. This data suggests that CO_2 laser treatment is more effective in preventing the recurrence of melasma compared to topical tranexamic acid. The lower recurrence rate in the CO_2 laser group may indicate a more sustained and lasting treatment effect, which could be a crucial factor for patients considering long-term outcomes and the likelihood of melasma returning after treatment.

Table 4: Comparing of recurrence rates between melasma patients who received CO_2 laser versus topical tranexamic acid

Recurrence	Melasma patients			
	Received CO_2 laser (N: 40)		Received topical tranexamic acid (N: 40)	
	No.	%	No.	%
Yes	7	18%	12	30%
No.	33	83%	28	70%
Total	40	100%	40	100%

P-value: 0.18

3.5 Comparing of side effects between melasma patients who received CO_2 laser versus topical tranexamic acid
The study showed that there are significant differences in side effects between melasma patients who received CO_2 laser treatment and those who were treated with topical tranexamic acid. Notably, none of the patients in the CO_2 laser group experienced post-inflammatory hyperpigmentation, while a substantial 30% (12 patients) in the tranexamic acid group did. Additionally, dryness and transient irritation were more prevalent in the tranexamic acid group (15% or 6 patients) compared to the CO_2 laser group (10% or 4 patients). Furthermore, a majority of patients in the CO_2 laser group reported no side effects (90% or 36 patients), which is significantly higher than the 55% (22 patients) in the tranexamic acid group. The overall side effects were significantly fewer in the CO_2 laser group, as indicated by the P-value of 0.003. This suggests that CO_2 laser treatment is associated with a lower incidence of side effects compared to topical tranexamic acid, highlighting its relative safety and tolerability for melasma patients.

Table 5: Comparing of side effects between melasma patients who received CO_2 laser versus topical tranexamic acid

Side effects	Melasma patients			
	Received CO_2 laser (n:40)		Received topical tranexamic acid (n:40)	
	No.	%	No.	%
Post inflammatory hyperpigmentation	0	0%	12	30%
Dryness, transient irritation	4	10%	6	15%
Non	36	90%	22	55%
Total	40	100%	40	100%

P-value: 0.003

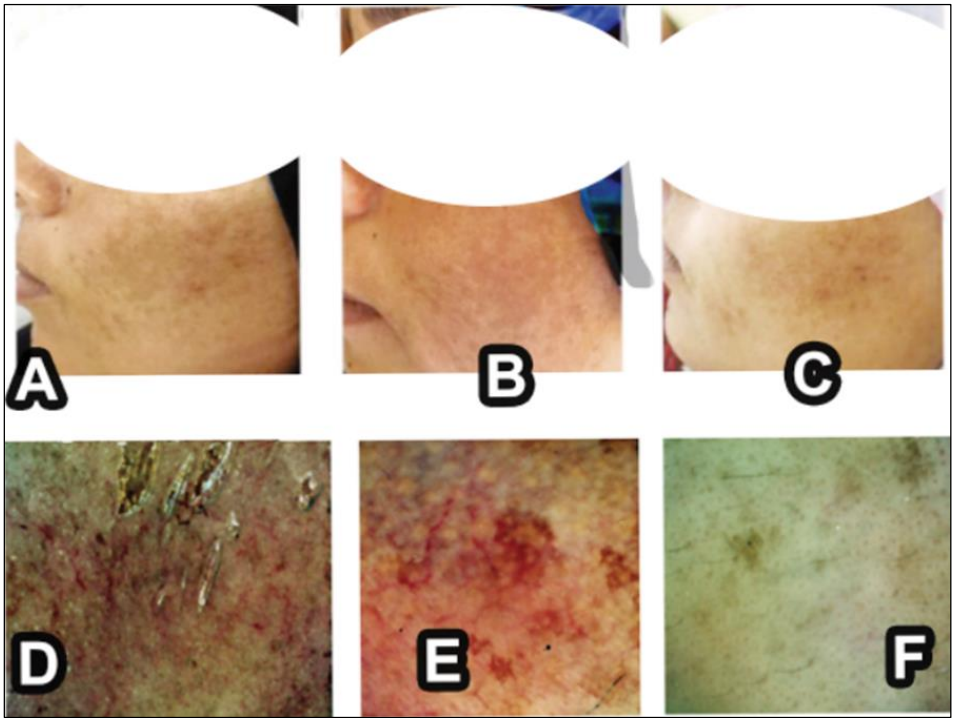
3.6 Dermoscopic Features
According to pigment color depth and morphological characteristics, several dermoscopic types of melasma were differentiated in two groups before treatment.

1. **Epidermal Type (Fig 2):** At low magnification, the background shows light brown patches. At high magnification, there are arcuate, honeycomb, and pseudo-reticular structures with unclear pigmentation patterns.
2. **Telangiectasia Type (Fig 3):** The vascular pattern includes dotted, dendritic, branched, and reticular structures, as well as amorphous structures. The vascular distribution pattern is mostly around brown macules and the pseudo-reticular pigment network.

More detailed observations include visible dry and scattered white scales, brown solar lentigo, and crescent-shaped and irregular radial dark brown spots around hair follicles. Some patients exhibited longer and thicker vellus hair. Under a higher power skin microscope, telangiectasia at different levels was found in nearly all melasma lesions, regardless of the clinically diagnosed types (Figures 3.2D and 3.3D).

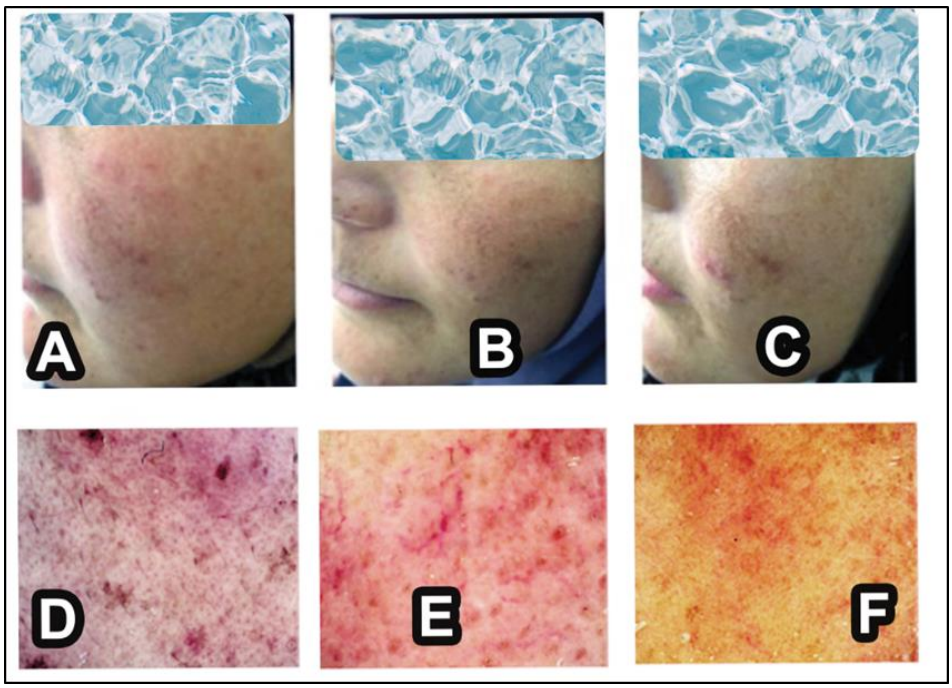
3.7 Post-Treatment Dermoscopic Examination
After the treatments, the dermoscopic examination of melasma is illustrated in Figures 3.2F and 3.3F. The overall background color becomes brighter and smoother, with fewer brown spots and remaining pigments scattered locally. Hair follicles are yellowed, and the number of pigment spots

is significantly reduced. The arrangement of hair follicles and sweat pores is more uniform compared to before the treatments. Most of the capillary networks splinter and turn into burnt reddish-brown spots.



a) Clinical picture receiving CO_2 laser treatment
b) Clinical picture after 8 of week of treatment
c) m MASI at follow-up of 16 weeks
d) Dermoscopic picture of before receiving CO_2 laser treatment
e) Dermoscopic picture in high power microscopic details
f) Dermoscopic picture after 12 of week receiving CO_2 laser treatment

Fig 2: Epidermal type melasma in a 33 -year- old Women



a) Clinical picture receiving CO_2 laser treatment.
b) Clinical picture after 8 of week of treatment.
c) m MASI at follow-up of 16 weeks.
d) Dermoscopic picture of before receiving CO_2 laser treatment.
e) Dermoscopic picture in high power microscopic details.
f) Dermoscopic picture after 12 of week receiving CO_2 laser treatment.

Fig 3: Telangiectasia type melasma in a 31 -year- old Women

5. Discussion

Melasma is a condition in which there is an abnormality in the production of melanin in humans, leading to the development of dark patches on the skin that are long-lasting and acquired over time. It manifests on regions of the body that are exposed to the sun and primarily impacts adult females [1]. The etiology of melasma is caused by several factors. The primary contributing variables include of unprotected sun exposure [10], visible light [11], hormonal changes due to pregnancy and oral contraceptive pill usage [12], stress and depression [13], and hereditary factors [14]. Melasma is a prevalent and acquired form of symmetrical melanoma. The patient's quality of life is adversely affected, and the therapies provide unsatisfactory results. Melasma is a multifaceted condition influenced by several causes, mostly centered on inflammation, reactive oxygen species, UV rays, hereditary factors, and hormones.

The findings of this study provide significant insights into the comparative effectiveness of CO_2 laser and topical tranexamic acid treatments for melasma. The results demonstrate a superior efficacy of CO_2 laser treatment in reducing melasma severity, enhancing patient satisfaction, and minimizing recurrence rates, with a favorable side effect profile compared to topical tranexamic acid. These findings align with existing literature and emphasize the potential benefits of CO_2 laser treatment in clinical practice.

At baseline, the mean MASI scores were comparable between the two groups, indicating similar severity of melasma before treatment initiation. As the treatment progressed, the CO_2 laser group showed significantly greater improvements in MASI scores starting from the 8-week mark. This trend continued through 12 and 16 weeks, highlighting the superior efficacy of CO_2 laser treatment in reducing melasma severity over time. These findings are consistent with previous study done by Qu *et al*. [15] that have reported the effectiveness of CO_2 laser in managing melasma by targeting and breaking down pigment deposits in the skin. Our findings align with those of Tawfic *et al*. [16], who observed a significant reduction in the MASI score after treatment. The treatments included fractional CO_2 laser alone as compare with TXA treatment, either topically or via intradermal injection.

The comparison of patient satisfaction between the two treatment groups revealed distinct differences. A significantly higher proportion of patients treated with CO_2 laser reported being very satisfied with their treatment outcomes. This contrasts with the more moderate satisfaction levels observed in the tranexamic acid group, where patients were more evenly distributed among the satisfied and slightly satisfied categories [18]. Several investigations have shown that fractional CO_2 laser may effectively treat melasma [19]. Melasma therapy has reportedly improved with the advent of fractional resurfacing, which has reduced the occurrence of post-inflammatory hyperpigmentation [20]. A significantly higher proportion of patients treated with CO_2 laser reported being very satisfied with their treatment outcomes than [21].

The CO_2 laser group had much lower recurrence rates than the tranexamic acid group. This means that CO_2 laser treatment may be able to keep melasma from coming back for a longer time. The lower risk of recurrence is very important for patients and doctors who are thinking about how the treatment will work in the long run. Previous studies have also found that laser treatments are better at keeping melasma under control than cosmetic treatments [18]. According to Trelles *et al*. [22], CO_2 laser therapy for melasma was more effective than topical lightening cream and the results lasted for up to a year after treatment. El Sinbawy *et al*. [23]. They looked at the effects of fractional CO_2 laser on facial melasma both clinically and microscopically in eleven melasma patients who were treated with two sessions of fractional CO_2 laser one month apart. They came to the conclusion that using low energy fractional CO_2 laser on melasma skin over and over again may lead to long-lasting improvement because it kills melanocytes. It was stated that there were no scars or changes in color after the inflammation. The study showed that the side effects profiles of the two types of medicine were very different. The CO_2 laser group had fewer side effects, and there were no reports of post-inflammatory discoloration. On the other hand, a lot of people who were treated with tranexamic acid had side effects like dryness and short-term inflammation, as well as post-inflammatory hyperpigmentation. The fact that the tranexamic acid group had more side effects shows that CO_2 laser treatment is generally safe and well-tolerated. These findings are in line with other research that shows laser treatments, when done correctly, may have fewer side effects than some cosmetic medicines [24]. The fractional CO_2 laser effectively gets rid of surface pigmentation, speeds up the breakdown of pigment, and finally creates a uniform skin tone. By using soft and regular pigment particle blasting, the particles can be made smaller, which makes them easier for macrophages to eat [25].

Exams of the skin through a microscope before and after treatment showed that people who got CO_2 laser treatment had much better-looking skin. Less brown spots showed up on the background, and the hair shafts and sweat pores were spread out more evenly. The general color got brighter and smoother. These changes show that the pigmentation was removed effectively and the skin's structure was improved. This is in line with what we already know about laser treatments for skin renewal [26].

6. Conclusion

1. The two groups had similar mean MASI scores at the start of the study, which means that the melasma was about as bad before treatment.
2. Over time, the MASI scores of the CO_2 laser group dropped significantly more, especially after 8 weeks. This suggests that the laser was more effective at decreasing the intensity of the melasma.
3. More patients in the CO_2 laser group said they were very pleased, which means they were happier with their care.
4. The group that used the CO_2 laser had much lower rates of return, which suggests that the treatment worked better and longer at keeping the melasma from coming back.
5. Post-inflammatory discoloration didn't happen in the CO_2 laser group, but patients who were treated with external tranexamic acid were more likely to experience dryness and short-term discomfort.
6. Most of the people in the CO_2 laser group said they had no side effects, which shows that this treatment is safer and easier to handle than external tranexamic acid.
7. Before treatment, dermoscopic exams showed different types of melasma, such as epidermal and telangiectasia

types, which are defined by their unique color and blood vessel patterns.
8. After the treatment, dermoscopic exams showed that the skin looked better, with fewer brown spots and a more even distribution of hair shafts and sweat pores. The background was brighter and smoother.

7. References

1. Sarkar R, Ghunawat S, Narang I, Verma S, Garg VK, Dua R, *et al*. Role of broad-spectrum sunscreen alone in the improvement of melasma area severity index (MASI) and Melasma Quality of Life Index in melasma. J Cosmet. Dermatol. 2019 Aug;18(4):1066-1073.
2. Yeung H, Kahn B, Ly BC, Tangpricha V. Dermatologic conditions in transgender populations. Endocrinol Metab Clin North Am. 2019 Jun;48(2):429-440.
3. Ching D, Amini E, Harvey NT, Wood BA, Ardakani MN. Cutaneous tumoural melanosis: A presentation of complete regression of cutaneous melanoma. Pathology. 2019 Jun;51(4):399-404.
4. Roberts WE, Henry M, Burgess C, Saedi N, Chilukuri S, Campbell-Chambers DA. Laser treatment of skin of color for medical and aesthetic uses with a new 650-microsecond Nd 1064 nm laser. J Drugs Dermatol, 2019 Apr 1, 18(4).
5. Rendon MI. Hyperpigmentation disorders in Hispanic population in the United States. J Drugs Dermatol, 2019 Mar 1, 18(3).
6. Zubair R, Lyons AB, Vellaichamy G, Peacock A, Hamzavi I. What's new in pigmentary disorders? Dermatol Clin. 2019 Apr;37(2):175-181.
7. Passeron T, Genedy R, Salah L, Fusade T, Kositratna G, Laubach HJ, *et al*. Laser treatment of hyperpigmented lesions: position statement of the European Society of Laser in Dermatology. J Eur. Acad. Dermatol Venereol. 2019 Jun;33(6):987-1005.
8. Kwon SH, Na JI, Choi JY, Park KC. Melasma: updates and perspectives. Exp Dermatol. 2019 Jun;28(6):704-708.
9. Juhasz MLW, Levin MK. The role of systemic treatments for skin lightening. J Cosmet. Dermatol. 2018 Dec;17(6):1144-1157.
10. Dinulos JG. Habif's Clinical Dermatology E-Book. Elsevier Health Sciences; c2019 Dec 10.
11. Tian B. The Asian problem of frequent laser toning for melasma. J Clin. Aesthet. Dermatol. 2017 Jul;10(7):40-42.
12. Wolverton SE, Wu JJ. Comprehensive dermatologic drug therapy. Elsevier Health Sciences; c2019 Dec 14.
13. Fatima S, Braunberger T, Mohammad TF, Kohli I, Hamzavi IH. The role of sunscreen in melasma and postinflammatory hyperpigmentation. Indian J Dermatol. 2020 Jan;65(1):5.
14. Morris-Jones R, editor. ABC of Dermatology. John Wiley & Sons; c2019 Sep 10.
15. James WD, Elston DM, Treat JR, Rosenbach MA, Neuhaus I. Andrews' Diseases of the Skin E-Book: Clinical Dermatology; c2021.
16. Feng X, Su H, Xie J. Efficacy and safety of tranexamic acid in the treatment of adult melasma: An updated meta-analysis of randomized controlled trials. J Clin. Pharm Ther. 2021;46(5):1263-1273.
17. Grimes PE, Ijaz S, Nashawati R, Kwak D. New oral and topical approaches for the treatment of melasma. Int. J Womens. Dermatol. 2018;5(1):30-36.
18. da Cunha MG, da Silva Urzedo AP. Melasma: A review about pathophysiology and treatment. Pigment Disord; c2022 Dec 22.
19. Phansuk K, Vachiramon V, Jurairattanaporn N, Chanprapaph K, Rattananukrom T. Dermal pathology in melasma: An update review. Clin. Cosmet. Investig. Dermatol. 2022 Jan 6;11:1-9.
20. Liu W, Chen Q, Xia Y. New mechanistic insights of melasma. Clin. Cosmet. Investig. Dermatol. 2023 Dec 31;16:429-442.
21. Hoque F, McGrath J, Shaude SE. Melasma (chloasma): pathogenesis and treatment. J Biotechnol. Biomed. 2022;5(4):236-243.
22. Piętowska Z, Nowicka D, Szepietowski JC. Understanding melisma - how can pharmacology and cosmetology procedures and prevention help to achieve optimal treatment results? A narrative review. Int. J Environ Res. Public Health. 2022 Sep 24;19(19):12084.
23. Kheradmand M, Afshari M, Damiani G, Abediankenari S, *et al*. Melasma and thyroid disorders: A systematic review and meta-analysis. Int. J Dermatol. 2019;58(11):1231-1238.
24. Rajanala S, Maymone MBC, Vashi NA. Melasma pathogenesis: A review of the latest research, pathological findings, and investigational therapies. Dermatol Online J. 2019;25(10):1-6.